WHITE PAPER NO. 12 – HUDSON RIVER RECORD OF DECISION
PCB CARCINOGENICITY WHITE PAPER

Response to a Review of

DRAFT BASELINE HUMAN HEALTH AND ECOLOGICAL RISK ASSESSMENT FOR THE LOWER FOX RIVER AND GREEN BAY, WISCONSIN REMEDIAL INVESTIGATION AND FEASIBILITY STUDY

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The white paper contained in this attachment was prepared as part of the Record of Decision for the Hudson River in New York. The topic of focus – PCBs as carcinogens – has relevance to the Lower Fox River and Green Bay site and the response to comments received on the Baseline Human Health and Ecological Risk Assessment and are defended by WDNR and EPA.

PCB CARCINOGENICITY (ID362702)

ABSTRACT

EPA classifies PCBs as probable human carcinogens based on data showing that PCBs cause cancer in animals and inadequate but suggestive evidence that PCBs cause cancer in humans. EPA's guidelines for classifying the carcinogenicity of chemicals are consistent with the approaches used by other national and international agencies. Moreover, EPA's Weight of Evidence classification of PCBs as probable human carcinogens has been externally peer reviewed and is equivalent to the classifications of the National Toxicology Program, the National Institute of Occupational Safety and Health, and the International Agency for Research on Cancer, part of the World Health Organization.

In the Human Health Risk Assessment for the Hudson River PCBs Site, EPA used the current externally peer-reviewed toxicity values for PCB carcinogenicity (i.e., cancer slope factors) contained in the Integrated Risk Information System, which is the Agency's consensus database of toxicity information. In the Human Health Risk Assessment, EPA summarized recent human epidemiological studies published since the 1996 PCB Cancer Reassessment. Based on a review of these newer studies, EPA determined that no change was necessary to EPA's classification of PCBs as probable human carcinogens. In the Human Health Risk Assessment, cancer risks from dioxin-like PCBs were calculated using current Toxicity Equivalency Factors developed by the World Health Organization. EPA submitted the Human Health Risk Assessment for external peer review. The peer reviewers agreed with the toxicity values EPA used in the Human Health Risk Assessment.

INTRODUCTION

The purpose of this paper is to provide an overview of EPA's process for evaluating the carcinogenicity of a chemical, development of cancer slope factors for PCBs, and the application of this toxicity information in the Human Health Risk Assessment for the Hudson River PCBs Site.

This paper is divided into four parts. The first part describes the history and development of the Agency's guidelines for carcinogenicity (USEPA, 1976, 1980, 1983a,b, 1984,

1986, 1994, 1996a, 1999a). Specific issues addressed in the guidelines include EPA's PCB Weight of Evidence classification, procedures for evaluating human epidemiological evidence and animal toxicity studies, and the use of this information in classifying the carcinogenicity of a chemical. The second part of this paper describes the Agency's evaluation of the carcinogenicity of PCBs. It summarizes the important human epidemiological and animal studies evaluated during the 1996 Cancer Reassessment for PCB carcinogenicity (USEPA, 1996b), presents some of the new information on the cancer toxicity of PCBs evaluated by EPA since 1996, and presents the current cancer slope factors in the Integrated Risk Information System (IRIS), the Agency's consensus database of toxicity information (USEPA, 1999b).

The third part provides a list of published papers describing some of the PCB toxicity research conducted by EPA scientists in the past 5 years, including studies of the mechanisms by which PCBs cause cancer and other adverse health effects.

The fourth part of this paper addresses the use of PCB cancer toxicity information in the Human Health Risk Assessment (HHRA) for the Hudson River PCBs Site (USEPA, 2000a–d). Specifically, this section discusses the use of cancer toxicity information (e.g., cancer slope factors) in IRIS and the toxic equivalency factors (TEFs) for dioxin-like PCBs. This section also describes the Agency's rationale for not using blood PCB levels in workers to evaluate cancer risks for people who eat PCB-contaminated fish from the Hudson River.

DEVELOPMENT OF EPA CARCINOGEN GUIDELINES

EPA's Carcinogen Guidelines (USEPA, 1976, 1983a,b, 1984, 1986, 1994, 1996a, 1999a) were used in determining the carcinogenicity of PCBs. These guidelines provide EPA's general framework for evaluating the cancer toxicity data (human and animal) for determining the Weight of Evidence classifications and cancer slope factors of chemicals. The Carcinogen Guidelines were developed after an evaluation of the procedures used by the International Agency for Research on Cancer (IARC), which is part of the World Health Organization (WHO) and the National Toxicology Program (NTP), which is part of the National Institutes of Health. In 1976, EPA issued interim procedures and guidelines for health risks and economic impact assessments of suspected carcinogens (USEPA, 1976). In 1979, the Interagency Regulatory Liaison Group held a meeting regarding carcinogens and methods for evaluating the technical adequacy of animal toxicity studies (IRLG, 1979).

In 1982, IARC issued a monograph on the evaluation of the carcinogenic risk of chemicals to humans (IARC, 1982). In 1984, NTP's Ad Hoc Panel on Chemical Carcinogenesis Testing and Evaluation issued a report regarding selection of dose levels for long-term animal studies (NTP, 1984).

In 1984, EPA began its work on the Guidelines for Carcinogen Risk Assessment (EPA, 1984). Draft guidelines were developed by a workgroup composed of expert scientists from throughout the Agency. The draft was externally peer reviewed by expert scientists in the field of carcinogenesis and related scientific disciplines, from universities,

environmental groups, industry, labor, and other governmental agencies. The guidelines were then proposed for public comment in the Federal Register (EPA, 1984).

In 1986, EPA issued the Guidelines for Carcinogen Risk Assessment (September 24, 1986), which are the product of a 2-year Agency-wide effort, which has included many scientists from the larger scientific community (USEPA, 1986). These guidelines incorporated comments and responses to external peer review comments and comments from the Agency's Science Advisory Board and were finalized and published in the Federal Register (USEPA, 1986). The guidelines incorporate information from the previous documents and also information and procedures used by NTP and IARC (e.g., the Weight of Evidence classification is based on the IARC approach). The 1986 Guidelines incorporated principles of the science for chemical carcinogens issued by the Office of Science and Technology Policy in 1985 (OSTP, 1985).

On April 23, 1996, the Proposed Guidelines for Carcinogen Risk Assessment were published in the Federal Register (USEPA, 1996a) for a 120-day public review and comment period. The Proposed Carcinogen Guidelines are a revision of EPA's 1986 Guidelines for Carcinogen Risk Assessment (USEPA, 1986) and, when final, will replace the 1986 cancer guidelines (USEPA, 1996a). The full text of the Federal Register notice is available on the web at www.epa.gov/ncea/.

Changes since the 1986 Carcinogen Guidelines (USEPA, 1986) are summarized in the 1996 Proposed Carcinogen Guidelines (USEPA, 1996a), as follows:

> "Since the publication of the 1986 cancer guidelines, there is a better understanding of the variety of ways in which carcinogens can operate. Today, many laboratories are moving toward adding new test protocols in their programs directed at mode of action questions. Therefore, the Proposed Guidelines provide an analytical framework that allows for the incorporation of all relevant biological information, recognize a variety of situations regarding cancer hazard, and are flexible enough to allow for consideration of future scientific advances."

In 1999, EPA proposed revised Carcinogen Guidelines (USEPA, 1999a) in response to comments by the EPA Science Advisory Board. The approaches outlined in the proposed revised guidelines are consistent with the 1996 Cancer Reassessment for PCBs (USEPA, 1996a). The 1999 proposed guidelines were developed to address issues regarding children's risk from exposure to carcinogens. On November 21, 2001, EPA published an announcement in the Federal Register soliciting additional scientific information and comments on the draft revised Carcinogen Guidelines that could assist EPA in completing the final Guidelines (USEPA, 2001). This Federal Register notice also stated that, until final Guidelines are issued, the July 1999 draft revised Guidelines will serve as EPA's interim guidance to EPA risk assessors preparing cancer risk assessments.

As outlined above, the carcinogenicity guidelines were developed within the Agency, published in the Federal Register for comment, and externally peer-reviewed. EPA responded to comments on the proposed guidelines and made changes based on a review of the comments submitted by these groups and individuals. The guidelines were also submitted for review to EPA's Science Advisory Board, an external scientific review panel.

EPA'S EVALUATION OF PCB CARCINOGENICITY

EPA classified PCBs as probable human carcinogens in 1988 (USEPA, 1988) and reaffirmed this classification in 1996 (USEPA, 1996b). EPA's classification is based on a weight of the evidence. The available classifications for chemicals are: (a) carcinogenic to humans, (b) probably carcinogenic to humans, (c) possibly carcinogenic to humans, (d) not classifiable as to human carcinogenicity, and (e) evidence of non-carcinogenicity to humans. The EPA classification of PCBs as probable human carcinogens is equivalent to the NTP, NIOSH, and IARC classifications for PCBs (NTP, 1981, 2000; NIOSH, 1977; IARC, 1978, 1987).

Following the 1988 evaluation of the carcinogenicity of PCBs, EPA conducted a reassessment of the carcinogenicity of PCBs in 1996 (USEPA, 1996b, see also www.epa.gov/ncea). In developing EPA's cancer reassessment for PCBs, EPA circulated the document within the Agency to more than 40 expert Agency scientists who reviewed and commented on the document. In addition, the document was submitted for external peer review to a panel of 16 experts in various areas of PCB toxicity, exposure, and carcinogenicity including a scientist from the General Electric Company (USEPA, 1996b,c). The panel agreed with EPA's conclusions (USEPA, 1996b,c) regarding the carcinogenicity of PCBs and recommended that the Agency use the Brunner et al. (1996) study to develop the cancer slope factor for PCBs. Following review by the Agency and a panel of external reviewers (Koller, 1996), EPA used data from the Brunner et al. (1996) study in the 1996 PCB Cancer Reassessment (USEPA, 1996b). This information was also incorporated into the IRIS file for PCBs (USEPA, 1999b), submitted to Congress in October 1996 and published in an article by the Agency's lead author of the 1996 PCB Cancer Reassessment (Cogliano, 1998).

The 1996 PCB Cancer Reassessment was conducted consistent with the 1996 Proposed Cancer Guidelines (USEPA, 1996a, pp. 6, 55–56), as follows:

> "This new assessment adopts a related approach that distinguishes among PCB mixtures by using information on environmental processes. Environmental processes have profound effects that can decrease or increase toxicity, so toxicity of an environmental mixture is only partly determined by the original commercial mixture. This new assessment, therefore, considers all cancer studies (which used commercial mixtures only) to develop a range of dose-response slopes, then uses information on environmental processes to provide guidance on choosing an appropriate slope for representative classes of environmental mixtures and different exposure pathways."

The 1996 PCB Cancer Reassessment is also consistent with the 1999 Revised Carcinogen Guidelines, which address children's health (USEPA, 1999a). EPA considered data from human epidemiological studies and animal studies in determining that PCBs are probable human carcinogens. In 1988, EPA concluded there was inadequate but suggestive evidence that PCBs cause cancer in humans and sufficient evidence that PCBs cause cancer in animals (USEPA, 1988). In 1996, EPA reaffirmed this classification, concluding (USEPA, 1996b), "Overall, the human studies have been considered to provide limited…to inadequate…evidence of carcinogenicity. The animal studies, however, have been considered to provide sufficient evidence of carcinogenicity" (USEPA, 1996b).

Human Epidemiological Studies

The peer reviewers of EPA's 1996 PCB Cancer Reassessment found inadequacies in the epidemiological data with regard to limited cohort size, problems in exposure assessment, lack of data on confounding factors, and the fact that occupational exposures may be to different congener mixtures than found in environmental exposures. The peer reviewers stated (USEPA, 1996c):

> "Most researchers think that PCBs act mainly as tumor promoters. Thus, at nontoxic doses, PCBs might be expected to increase cancer risk mainly in humans that have sustained cancer initiation due to exposure to genotoxicants or to the presence of a mutant gene. For common cancers that have complex and multiple etiologies, promotive effects will be seen by epidemiology only if specifically looked for. Epidemiological studies have not thus far tested this hypothesis."

EPA has summarized the human epidemiological studies used to classify PCBs as probable human carcinogens (USEPA, 1996b, 1999b). The human epidemiological evidence is described in USEPA (1999b) as follows (SMR = standard mortality ratio, CI = confidence interval, p = level of statistical significance):

> "Inadequate. A cohort study by Bertazzi et al. (1987) analyzed cancer mortality among workers at a capacitor manufacturing plant in Italy. PCB mixtures with 54%, then 42% chlorine were used through 1980. The cohort included 2100 workers (544 males and 1556 females) employed at least 1 week. At the end of follow-up in 1982, there were 64 deaths reported, 26 from cancer. In males, a statistically significant increase in death from gastrointestinal tract cancer was reported, compared with national and local rates (6 observed, 1.7 expected using national rates, SMR = 346, CI = 141–721; 2.2 expected using local rates, SMR = 274, CI = 112–572). In females, a statistically significant excess risk of death from hematologic cancer was reported, compared with local, but not national, rates (4 observed, 1.1 expected, SMR = 377, CI = 115–877). Analyses by exposure duration, latency, and year of first exposure revealed no trend; however, the numbers are small. A cohort study by Brown (1987) analyzed cancer mortality among workers at two capacitor manufacturing plants in New York and Massachusetts. At both plants the Aroclor mixture being used changed twice, from 1254 to 1242 to 1016. The cohort included 2588 workers (1270 males and 1318 females) employed at least 3 months in areas of the plants considered to have potential for heavy exposure to PCBs. At the end of follow-up in 1982, there were 295 deaths reported, 62 from cancer. Compared with national rates, a statistically significant increase in death from cancer of the liver, gall bladder, and biliary tract was reported (5 observed, 1.9 expected, SMR = 263, $p < 0.05$). Four of these five occurred among females employed at the Massachusetts plant. Analyses by time since first employment or length of employment revealed no trend; however, the numbers are small.
>
> A cohort study by Sinks et al. (1992) analyzed cancer mortality among workers at a capacitor manufacturing plant in Indiana. Aroclor 1242, then 1016, had been used. The cohort included 3588 workers (2742 white males and 846 white females) employed at least 1 day. At the end of follow-up in 1986, there were 192 deaths reported, 54 from cancer. Workers were classified into five exposure zones based on distance from the impregnation ovens. Compared with national rates, a statistically significant excess risk of death from skin cancer was reported (8 observed, 2.0 expected, SMR = 410, CI = 180–800); all were malignant melanomas. A proportional hazards analysis revealed no pattern of association with exposure zone; however, the numbers are small. Other occupational studies by NIOSH (1977), Gustavsson et al. (1986) and Shalat et al. (1989) looked for an association between occupational PCB exposure and cancer mortality. Because of small sample sizes, brief follow-up periods, and confounding exposures to other potential carcinogens, these studies are inconclusive. Accidental ingestion: Serious adverse health effects, including liver cancer and skin disorders, have been observed in humans who consumed rice oil contaminated with PCBs in the "Yusho" incident in Japan or the "Yu-Cheng" incident in Taiwan.

> These effects have been attributed, at least in part, to heating of the PCBs and rice oil, causing formation of chlorinated dibenzofurans, which have the same mode of action as some PCB congeners (ATSDR, 1993; Safe, 1994)."

Animal Data

EPA determined that PCBs cause cancer in animals based on animal bioassay data. The NTP and IARC also conclude that PCBs are animal carcinogens (NTP, 1981; IARC, 1987). ATSDR's Toxicological Profile (ATSDR, 2000) states, "there is conclusive evidence that commercial PCB mixtures are carcinogenic in animals based on induction of tumors in the liver and thyroid." EPA's evaluation (USEPA, 1996b, 1999b) of the animal bioassay data for PCBs is summarized below:

> "A 1996 study found liver tumors in female rats exposed to Aroclors 1260, 1254, 1242, and 1016, and in male rats exposed to 1260. These mixtures contain overlapping groups of congeners that, together, span the range of congeners most often found in environmental mixtures. Earlier studies found high, statistically significant incidences of liver tumors in rats ingesting Aroclor 1260 or Clophen A 60 (Kimbrough et al., 1975; Norback and Weltman, 1985; Schaeffer et al., 1984). Mechanistic studies are beginning to identify several congeners that have dioxin-like activity and may promote tumors by different modes of action. PCBs are absorbed through ingestion, inhalation, and dermal exposure, after which they are transported similarly through the circulation. This provides a reasonable basis for expecting similar internal effects from different routes of environmental exposure. Information on relative absorption rates suggests that differences in toxicity across exposure routes are small."

Varying Dose Levels Tested

EPA evaluated a number of animal bioassays regarding the carcinogenicity of PCBs that were conducted at varying dose levels, not only at the Maximum Tolerated Dose (MTD). Consistent with NTP and IARC protocols (NTP, 1984; IARC, 1982, 1987), animal studies are conducted at varying levels below the MTD to aid in establishing a dose-response curve. Data at or near the MTD level were evaluated consistent with EPA's 1986 Carcinogen Guidelines (USEPA, 1986), which state: "Long-term animal studies at or near the MTD are used to ensure an adequate power for the detection of carcinogenic activity."

EPA's 1996 PCB Cancer Reassessment (Table 2-1, USEPA, 1996b), which showed the liver tumor incidences in rats from lifetime exposure studies from 1975 to 1985, generally included a control group of rats not exposed to PCBs and other groups exposed to varying concentrations of PCBs (i.e., 25 ppm, 50 ppm, and 100 ppm). The cited studies include Kimbrough et al. (1975), NCI (1978), Schaeffer et al. (1984), and Norback and Weltman (1985). The Brunner et al. (1996) rat study (later published as Mayes et al., 1998) included doses of PCBs ranging from the control (0 ppm), to 25 ppm, 50 ppm, 100 ppm and 200 ppm. The Brunner et al. (1996) lifetime study data, in which rats were exposed to PCBs at levels less than the MTD for 104 weeks, demonstrated that the rats fed diets of PCBs had statistically significant, dose-related, increased incidences of liver tumors from each Aroclor mixture (USEPA, 1996b).

In addition, the partial lifetime studies that were evaluated by EPA also included exposures to various concentrations of PCBs. Kimbrough et al. (1972) included dose levels of 0 ppm, 20 ppm, 100 ppm, 500 ppm, or 1,000 ppm for Aroclor 1254 or 1260.

Other studies include Kimbrough and Linder (1974), in which BALB/cJ mice were exposed to 300 ppm of Aroclor 1254 for 11 months or for 6 months followed by 5 months without exposure to PCBs. Kimura and Baba (1973) exposed Donryu rats to diets ranging from 38 to 462 ppm of Kanechlor (a trade name for PCBs) 400. Ito et al. (1973) exposed dd mice to 0 ppm, 100 ppm, 250 ppm or 500 ppm of Kanechlor 300, 400 or 500. Ito et al. (1974) exposed Wistar rats to diets of 0, 100, 500, or 1,000 ppm of Kanechlor 300, 400, or 500 ppm. Rao and Banerji (1988) exposed male Wistar rats to diets of 0 ppm, 50 ppm or 100 ppm of Aroclor 1260.

Gender Differences in Tumors

EPA followed appropriate guidelines and policies in extrapolating the data from the Brunner et al. (1996) rat study to humans. As stated in the PCB Cancer Reassessment (USEPA, 1996b, see p. 44), "the different responses for male and female rats (Brunner et al., 1996) suggest the possibility of developing different potency values for males and females. In view of the 91% response in male Wistar rats (Schaeffer et al., 1984), as well as the sensitivity of male mice (Kimbrough and Linder, 1974; Ito et al., 1973), it is premature to conclude that females are always more sensitive. The PCB Cancer Reassessment (USEPA, 1996b) provides summary tables of the ranges of potency values based on data from both males and females. The potencies are based primarily on the range of Aroclors 1260, 1254, 1242 and 1016 tested in female Sprague-Dawley rats, but other studies were considered also.

Benign and Malignant Tumors

Consistent with the framework set forth in the Agency's Carcinogen Guidelines (USEPA, 1986, 1996a, 1999a), EPA considered benign as well as malignant tumors in evaluating the carcinogenicity of PCBs because both benign and malignant tumors are considered to be representative of related responses to the PCBs. Benign tumors progressed to malignant tumors in multiple studies.

EPA is not alone in using this approach to evaluate tumor data in assessing the carcinogenicity of chemicals. The Agency's 1996 proposed Carcinogen Guidelines (USEPA, 1996a) noted, "As in the approach of the National Toxicology Program and the International Agency for Research on Cancer, the default is to include benign tumors observed in animal studies in the assessment of animal tumor incidence if they have the capacity to progress to the malignancies with which they are associated. This treats the benign and malignant tumors as representative of related responses to the test agents, which is scientifically appropriate. This is a science policy decision that is somewhat more conservative of public health than not including benign tumors in the assessment. Nonetheless, in assessing findings from animal studies, a greater proportion of malignancy is weighed more heavily than a response with a greater proportion of benign tumors. Greater frequency of malignancy of a particular tumor type in comparison with other tumor responses observed in an animal study is also a factor to be considered in selecting the response to be used in dose response assessment."

With respect to PCB carcinogenicity, in 1996, EPA described a study by Norback and Weltman (1985) that demonstrated tumor progression as follows (USEPA, 1996b):

> "Norback and Weltman (1985). Groups of male or female Sprague-Dawley rats were fed diets with 0 or 100 ppm Aroclor 1260 for 16 months; the latter dose was reduced to 50 ppm for 8 more months. After 5 additional months on the control diet, the rats were killed and their livers were examined. Partial hepatectomy was performed on some rats at 1, 3, 6, 9, 12, 15, 18, and 24 months to evaluate sequential morphologic changes. In males and females fed Aroclor 1260, liver foci appeared at 3 months, area lesions at 6 months, neoplastic nodules at 12 months, trabecular carcinomas at 15 months, and adenocarcinomas at 24 months, demonstrating progression of liver lesions to carcinomas. By 29 months, 91 percent of females had liver carcinomas and 95 percent had carcinomas or neoplastic nodules; incidences in males were lower, 4 and 15 percent, respectively (see table 2–1)."

EPA also evaluated PCB carcinogenicity based on lifetime and stop studies of rats fed diets containing Aroclors 1260, 1254, 1242 or 1016, using data from Brunner et al. (1996). From the lifetime study data, in which rats were exposed to PCBs for 104 weeks, EPA concluded that the rats fed diets of PCBs had statistically significant, dose-related, increased incidences of liver tumors from each Aroclor mixture (USEPA, 1996b; Cogliano, 1998). From the stop study data, in which the rats were exposed to PCBs for 52 weeks and then PCB exposure was stopped, EPA determined that, for Aroclors 1254 and 1242, tumor incidences were approximately half those of the lifetime study; that is, nearly proportional to exposure duration. In contrast, for Aroclor 1016, stop-study tumor incidences were zero, while for Aroclor 1260 they were generally greater than half as many as in the lifetime study.

Earlier studies found high, statistically significant incidences of liver tumors in various strains of rats ingesting Aroclor 1260 or Clophen A60 (Kimbrough et al., 1975, Norback and Weltman, 1985; Schaeffer et al., 1984). Kimbrough et al. (1975) found significantly increased hepatocellular carcinomas in rats fed Aroclor 1260. Schaeffer et al. (1984) found male Wistar rats in the shortest exposed group (16.4 months) had preneoplastic liver lesions, and after 23 months had hepatocellular carcinomas. Norback and Weltman (1985) studied Sprague-Dawley rats exposed to Aroclor 1260 and found that by 29 months 91% of females had liver carcinomas. In addition, the Brunner et al. (1996) study found several of the tumors were hepatocholangiomas, a rare bile duct tumor seldom seen in control rats.

The data from the studies described above are the basis for EPA's determination that PCBs cause cancer in animals. Benign tumors progressed to malignant tumors in multiple studies, in different strains of rats, and at different dose levels of PCBs.

Cancer Slope Factor (CSF)

The quantification of carcinogenicity is a value called a cancer slope factor (CSF). As outlined in the EPA Carcinogen Guidelines (USEPA, 1986; 1996a), EPA favors basing CSFs on human epidemiological studies, which requires quantitative information on both exposure and response. However, for PCBs, EPA concluded that the human epidemiological data are insufficient to develop CSFs (USEPA, 1996b). During the peer review of EPA's 1996 PCB Cancer Reassessment (USEPA, 1996c), EPA included charge questions to the peer-reviewers requesting specific evaluation of human epidemiological evidence as a basis for developing the CSFs for PCBs. The peer reviewers supported EPA's conclusion that it is not feasible to use the human epidemiological data to develop

CSFs for PCBs (USEPA, 1996c). EPA used the proposed 1996 Carcinogen Guidelines (USEPA, 1996a) to develop the CSFs for PCBs. Following review of the carcinogenicity data and based primarily on the Brunner et al. (1996), EPA developed separate PCB CSFs for inhalation and ingestion, and provided a recommendation for exposure by dermal contact. The oral CSF for PCBs developed in 1988 (USEPA, 1988) was revised downward in 1996 from 7.7 mg/kg-day-1 to 2.0 mg/kg-day–1. In the 1996 PCB Cancer Reassessment (USEPA, 1996b, p. 35), EPA explained,

> "This difference in cancer slope factor is attributable to three factors, each responsible for reducing the slope by approximately one-third: the rat liver tumor reevaluation (Moore et al., 1994), use of the new cross-species scaling factor (USEPA, 1992) and not using a time weighted average dose."

Similarly, when these factors are applied to the CSF derived from the Norback and Weltman (1985) study, the CSF is reduced from 7.7 mg/kg-day–1 to 2.2 mg/kg-day-1.

As part of EPA's 1996 PCB Cancer Reassessment, EPA evaluated an approach regarding PCB congener persistence in the body (Brown, 1994). EPA identified some limitations of using this approach in the development of CSFs for PCBs, as follows (USEPA, 1996b):

> "Reconstruction of past exposure is problematic because different mixtures had been in use over the years, the distribution of exposure and absorption by route and congener is unknown, and congener persistence in the body varies greatly from congener to congener (Brown, 1994) and person to person (Steele et al., 1986)."

HUMAN EPIDEMIOLOGICAL STUDIES SINCE THE 1996 PCB CANCER REASSESSMENT

Since the 1996 PCB Cancer Reassessment (USEPA, 1996b), additional studies regarding the carcinogenicity of PCBs in humans have been published (e.g., Gustavsson and Hogstedt, 1997; Hardell et al., 1996; Rothman et al., 1997; Tironi et al., 1996; Yassi et al., 1994; Loomis et al., 1997; Kimbrough et al., 1999 [discussed separately]). EPA has noted issues with many of the studies of occupationally exposed individuals working in industrial plants in the U.S. and internationally (USEPA, 1996b). Issues include the small number of tumors found, making it difficult to associate the exposures with specific manufacturing processes in the plant studied by the investigators (i.e., high exposure, medium exposures, or low exposure areas); mortality rather than morbidity as a study objective; the lack of historical data on exposures; and confounding from exposures to chemicals other than PCBs within the plant. A brief summary of the studies and their conclusions regarding the carcinogenicity of PCBs is provided below by type of cancer and population studied.

Breast Cancer

Recent studies have investigated PCB exposures and breast cancer. EPA has evaluated these studies and concluded that it is not possible to attribute a cause and effect association between PCB exposure and breast cancer given the sparse data available (USEPA, 1997). Study results suggested that PCBs increase the risk of breast cancer

after menopause (Moysich et al., 1998) and research has suggested a mechanism by which PCBs can contribute to cancer, including breast cancer (Oakley et al., 1996). Other studies have failed to show an association between PCB exposure and breast cancer (e.g., Hoyer et al., 1998, see studies reviewed in USEPA, 1997 and Table D-1 of USEPA, 2000a).

Researchers have suggested the need to consider PCB levels in women prior to the time of breast cancer diagnosis (e.g., Adami et al., 1995). The critical or sensitive period of exposure for the developing breast tissue may be as an infant or during puberty, in which case the current procedure of measuring blood PCB levels at the time of diagnosis may not be an appropriate biomarker of exposure.

Organ Sites Excluding Breast Cancer

EPA has also evaluated studies on PCB exposures and cancers other than breast cancer. Based on the available epidemiological evidence, EPA believes that the data are inconclusive with respect to the association of PCBs and cancer in humans, including hepatobiliary, hematological, malignant melanoma, rectal, gastrointestinal tract, pancreatic, and endometrial cancers based on the limitations of the epidemiological studies (USEPA, 1999b).

Kimbrough et al. (1999a) Occupational Study

In 1999, Dr. Kimbrough and colleagues published a study of cancer mortality in workers exposed to PCBs (Kimbrough et al., 1999a). The paper describes a study of workers from two GE capacitor manufacturing plants in New York State. In this study, mortality (deaths) from all cancers was determined for 7,075 females and males who worked at the GE facilities for at least 90 days between 1946 and 1977. The total number of deaths from all causes was 1,195 people, and the total number of deaths caused by cancer was 353 people. No significant elevations in mortality for any site-specific cause were found in the hourly worker cohort (i.e., group). No significant elevations were seen in the most highly exposed workers. Mortality from all cancers was significantly below expected in hourly male workers and comparable to expected for hourly female workers. Several researchers submitted Letters to the Editor identifying limitations of the Kimbrough et al. (1999a) study, which were published in the Journal of Occupational and Environmental Medicine (Bove et al., 1999; Frumkin and Orris, 1999). The response to these letters was also published (Kimbrough et al. (1999b).

EPA performed a preliminary review of the Kimbrough et al. (1999a) study and identified aspects of the study that suggest that the study will not change the Agency's conclusions regarding the carcinogenicity of PCBs (USEPA, 2000a–c). The primary limitation, which is shared by other similar epidemiological studies, is that the degree of exposure is not well characterized. As part of its review, EPA sent copies of the Kimbrough et al. (1999a) paper to several researchers requesting an evaluation regarding whether this new paper would change the Weight of Evidence classification of PCBs as probable human carcinogens. The findings from these letters are summarized below:

Dr. D. Ozonoff of the Boston University School of Public Health concluded (Ozonoff, 1999):

> "In short, we have here another "data point". It should be judiciously interpreted and used with the caution appropriate to studies of this type. In particular, this means not giving undue weight to its failure to show associations previously revealed, since there are too many factors that would mitigate against being able to show them in this study."

Dr. M. Harnois of the Massachusetts Department of Environmental Protection concluded (Harnois, 1999):

> "A subgroup that is masked in this study is the one containing hourly male workers exposed to Aroclor 1254 by dermal contact, incidental ingestion, and inhalation for at least 5 years and followed for at least 20 years. This group could have different cancer frequencies from those presented in the report, being definitely exposed to a known carcinogenic mixture for a prolonged interval and observed for an interval that could allow development of tumors.
>
> This report deals mostly with deaths due to cancer effects, but we know that reproductive, nervous and immunological effects can also occur. These are beyond the scope of the research report, but may be ignored by readers who assume that cancer is the only effect of PCBs."

Dr. T. Mack of the University of Southern California, Norris Comprehensive Cancer Center concluded (Mack, 1999):

> "I guess my bottom line is that the summary statements ("lack of any significant elevations adds important information" and "lack of consistent findings—would suggest a lack of an association") in the paper are appropriate. I think that it is appropriate to downgrade the priority given to PCB's. However, based on the animal studies (and recognizing a. the possibility limited relevance to man and b. the absence of any confirmation of liver cancer in humans) and on this very small amount of information pointing to colorectal tumors, I don't think that this potential carcinogenicity of PCB's can be completely dismissed. I recognize the flimsiness of the evidence, and that a less conservative person could persuasively argue the other way."

The ATSDR Toxicological Profile for PCBs (ATSDR, 2000) summarizes the limitations of the exposure information from Kimbrough et al., (1999a) as follows:

> "PCB exposures were predominantly to Aroclor 1254 from 1946 to 1954, Aroclor 1242 from 1954 to 1971, and Aroclor 1016 from 1971 to 1977. Exposures were qualitatively classified as high, low, or undefinable based on types and locations of jobs and some area measurements. No personal exposure monitoring was performed, although previously reported data on 290 self-selected workers from one of the plants had serum PCBs levels in ranges of 6 to 2,530 and 1 to 546 ppb for lower and higher chlorinated homologs, respectively (Wolff et al., 1982). Workers with high exposure jobs had direct PCB contact (dermal and/or inhalation), workers with lower exposure jobs primarily had inhalation exposure to background levels of PCBs in the plant, and workers with undefinable exposures had exposures that varied depending on whether tasks were performed. Exposure-specific analysis was limited to workers with the greatest potential for exposure (i.e., hourly workers who ever worked in a high exposure job, worked for at least 6 months in a high-exposure job, worked for at least 1 year in a high-exposure job). Workers who exclusively worked in high-exposure jobs could not be analyzed as a separate group due to small numbers (112 males, 12 females)."

The Toxicological Profile for PCBs concluded (ATSDR, 2000):

> "Interpretation of the Kimbrough et al. (1999a) findings is complicated by a few study limitations and biases, including some exposure misclassifications related to use of length of employment alone as a surrogate of exposure, potentially insufficient dosage differences between exposed and

> comparison groups, a degree of selection bias due to the healthy worker effect that may have resulted in an under estimate of SMRs, concern for low statistical power due to the small number of deaths from site-specific cancers in some of the group (e.g., female hourly workers with high exposure and > 20 years latency), relatively young age at follow-up, and use of the general population for comparison rather than an internal control group or a group of workers from another company. These issues are discussed by Bove et al. (1999), Frumkin and Orris (1999), and Kimbrough et al., (1999b). Some of the limitations are typical of occupational cohort mortality studies, and strengths of the study include its size (the largest cohort of PCB workers ever studied) and essentially complete follow-up of long duration. Unresolved are the puzzling Kimbrough et al. (1999a) findings of significantly lower than expected mortality from all cancers among males and the lower number of observed cases of liver and biliary tract cancers among females compared to the smaller cohort studies by Brown et al. (1987), a subset of the same study population. These unresolved findings suggest that ascertainment of cancer mortality was not completed in this study. Overall, the study limitations are sufficient to cast doubt on the negative findings for liver and biliary tract cancer and other site-specific cancers."

In light of the information summarized above regarding the limitations of the Kimbrough et al. (1999a) study, which are similar to the limitations of other human epidemiological studies, EPA has not changed its Weight of Evidence classification of PCBs as probable human carcinogens.

EPA's PCB RESEARCH

EPA has conducted significant research on PCBs and the mechanisms of PCB action. Following is a partial list of research conducted by EPA's Office of Research and Development from 1996 to 2000. In addition, EPA has worked with other federal agencies through programs such as the Superfund Basic Research Program (part of the National Institute of Environmental Health Sciences) to fund research on PCB toxicity through grants to a number of Universities (Massachusetts Institute of Technology, State University of New York-Albany, University of Kentucky, etc.) that are evaluating PCB toxicity.

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HUDSON RIVER PCBS SITE

IRIS toxicity values undergo an extensive internal and external peer review process (USEPA, 1996b,c and 1999b) and are thus the preferred toxicity values for use in Superfund risk assessments (USEPA, 1989, 1993, 1996b,c). The use of IRIS data in the evaluation of the toxicity of chemicals at Superfund sites addresses EPA's goal of using consistent toxicity information in risk assessments at Superfund sites across the country.

Consistent with EPA's risk assessment guidance (USEPA, 1989, 1990, 1993), in the HHRA for the Hudson River PCBs Site, EPA evaluated newer studies of PCB toxicity (USEPA, 2000a,b). Based on this review, EPA determined that these newer studies would not change the conclusions of the 1996 PCB Cancer Reassessment (i.e., that PCBs are probable human carcinogens) and that it was appropriate to use the toxicity information and CSFs in IRIS in the Site-specific risk assessment (USEPA, 1996b,c; 2000a-d).

The peer reviewers for the HHRA agreed with EPA's use of the toxicity information in IRIS, but recommended that EPA provide an update of the data to identify recently published studies (ERG, 2000). In response, EPA updated the list of human

epidemiology studies in Appendix D of the Revised HHRA (USEPA, 2000a). EPA identified a number of limitations with these newer human epidemiological studies similar to those identified in the IRIS file for PCBs (USEPA, 1999a), including lack of sufficient exposure information, failure to adequately account for co-exposure to other compounds, and inconsistency between study results.

EPA recognizes that environmental processes can alter the congener composition of a PCB mixture in the environment. The CSFs in IRIS are based on studies using a number of different Aroclor mixtures (i.e., the commercial formulation of PCBs including Aroclor 1016, 1242, 1254, and 1260), which together span the range of congeners most frequently found in environmental mixtures (USEPA, 1996b). IRIS provides for using a lower CSFs for risk calculations when congener analysis demonstrates a predominance of the lower chlorinated congeners (i.e., when congener or isomer analysis verifies that congeners with more than four chlorine atoms comprise less than 1/2 percent of the total PCBs). This lower CSF was not used in the HHRA based on congener analysis of Hudson River fish.

Dioxin-Like PCBs

Consistent with EPA guidance and procedures (USEPA, 1996b), the revised HHRA (USEPA, 2000a) evaluated cancer risks from exposure to dioxin-like PCBs using the latest scientific consensus on TEFs for dioxin-like PCBs (USEPA, 1996b), as an additional consideration for the risk manager. Risks from dioxin-like PCBs were not combined with non-dioxin-like PCBs, based on EPA's ongoing effort to develop a procedure for combining these cancer risks to avoid potential double counting.

Effect of PCB Exposure on Blood Levels

EPA followed risk assessment guidance and procedures (USEPA, 1989, 1990, 1993, 1996b) to quantify cancer risks to individuals exposed to PCBs at the Hudson River PCBs Site in the HHRA (USEPA, 2000a). The approach used in the HHRA is different than measurement of blood PCB levels in former capacitor workers. First, the HHRA evaluates current and future exposures, while the data on PCB levels in blood integrates past exposure. Second, capacitor workers were primarily exposed through dermal contact and inhalation of PCBs, whereas anglers, which had the highest cancer risks evaluated in the HHRA, would be exposed to PCBs through ingestion of contaminated fish caught in the Hudson River. Third, in the HHRA EPA evaluated cancer risks to the RME individual, whereas for capacitor workers the level of exposure is generally not known. Fourth, the PCB congener profile in the capacitor plant is likely to be different from the congener profile of PCBs that are bioaccumulated in the fish. Lastly, EPA is concerned with potential exposures to the human population including sensitive groups that may include the fetus exposed from mothers who consumed PCB-contaminated fish, infants exposed to PCBs through breast milk, young children, adolescents, adults, and individuals with pre-existing medical conditions (USEPA, 2000a); many of these sensitive groups may not be represented in a healthy worker population. As stated in EPA's 1996 PCB Cancer Reassessment (USEPA, 1996b):

> "people with decreased liver function, including inefficient glucuronidative mechanism in infants, can have less capacity to metabolize and eliminate PCBs (Calabrese and Sorenson, 1977).

> Additionally, approximately 5% of nursing infants receive a steroid in human milk that inhibits the activity of glucuronyl transferase, further reducing PCB metabolism and elimination (Calabrese and Sorenson, 1977)."

Differences between occupational exposures and exposure through ingestion of contaminated fish were discussed in the 1996 PCB Cancer Reassessment (USEPA, 1996b). Notably, a study of people exposed through eating contaminated fish (Hovinga et al., 1993) suggests that the PCB mixtures in fish can be more persistent than those to which the workers were exposed. From 1977 to 1985, mean PCB serum levels (quantified using Aroclor 1260 as a reference standard) from 111 Great Lakes fish eaters decreased only slightly from 20.5 to 19.0 ppb. This indicates that the rate of decline in the fish eating populations will be slower than that for the workers. ATSDR's Toxicological Profile (ATSDR, 2000) states that there are no known treatment methods for reducing body burdens of PCBs, concluding that limiting or preventing further exposures appears to be the most practical method for reducing PCB body burdens.

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